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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **Anticonvulsant agents.**

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US-A- 4 379 165

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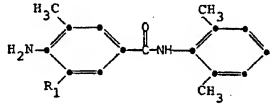
EP 0 211 568 B1

Description

The several anticonvulsant drugs marketed in the United States provide significant seizure relief for only 50–75% of epileptic patients. The therapeutic effects are sometimes accompanied by serious side effects such as sedation, ataxia, psychoses, suicidal depression, gastrointestinal disturbances, gingival hyperplasia, lymphadenopathies, megaloblastic anemias, hepatotoxicity, nephropathies, hirsutism, and fetal malformations. These side effects, which range in severity from mild sedation to death from aplastic anemia, are particularly troublesome since most of the marketed anticonvulsants have very low therapeutic ratios. For example, phenytoin, one of the most widely used anticonvulsants, controls seizures in man only when plasma levels reach 10 mcg/ml. Toxic effects such as nystagmus are seen at around 20 mcg/ml, ataxia is obvious at 30 mcg/ml, and lethargy is apparent at about 40 mcg/ml. See "The Pharmacological Basis of Therapeutics" (Gilman, Goodman, and Gilman, ed., 6th Ed., MacMillan Publishing Co., Inc., New York, New York (1980)), p. 455. In view of these facts, most epileptologists indicate there is a definite need for more selective and less toxic anticonvulsant drugs. Certain p-aminobenzoylarylamines are described in Compt. Rend., 259 (23), 4295 (1964).

This invention provides p-aminobenzamides of the formula I



I

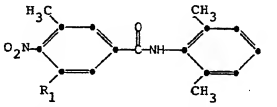
wherein

R_1 are each independently is hydrogen or methyl;

and pharmaceutically acceptable acid addition salts thereof.

According to a further aspect of the present invention, there are provided pharmaceutical formulations which comprise as active ingredient a benzamide of formula I in association with a pharmaceutically acceptable carrier or diluent.

This invention also provides compounds of the formula II



II

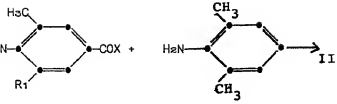
wherein

R_1 is the same as previously defined. These nitro derivatives are useful as intermediates for preparing the anticonvulsant p-aminobenzamides of formula I.

The present invention relates to organic compounds that are useful for treating and preventing convulsions in mammals.

The pharmaceutically acceptable acid addition salts of this invention can be prepared by standard methods known in the art employing those acids of sufficient acidity to form acid addition salts with the basic aniline group. These include salts derived from inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydriodic acid, phosphorous acid and the like, as well as salts derived from organic acids such as aliphatic mono- and di-carboxylic acids, phenyl-substituted alkanoic acids, hydroxy-alkanoic and -alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such pharmaceutically acceptable salts thus include sulfate, metaphosphate, pyrophosphate, chloride, bromide, iodide, fluoride, oxalate, maleate, benzenesulfonate, toluenesulfonate, chlorobenzenesulfonate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate and the like. The preferred salts are those derived from inorganic acids, especially hydrochloric acid.

The compounds of formula I may be prepared by any of several methods well known in the art. A preferred method comprises reacting a p-nitrobenzoyl halide III with an amine IV according to the general method as taught in U.S. Patent No. 4 379 165, and according to the following scheme:



III IV

wherein
X is a leaving group such as C_1–C_3 alkoxy or halo, especially chloro. The reaction follows the general procedure of reaction A in the above mentioned patent. It is preferred that a benzoyl halide and the amine be reacted in a non-reactive solvent, such as tetrahydrofuran, preferably in the presence of an acid scavenger such as a carbonate, especially potassium carbonate, or an organic base, such as triethylamine. Although it is preferred that the reactants be added in molar ratios of about 1.5:1.0 (III:IV), other ratios are completely operative. The reaction is carried out from about room temperature up to the reflux temperature of the reaction mixture. Under the preferred conditions of reflux, the reaction is generally complete in 1–12 hours.

The p-nitrobenzamides of the invention may be converted into the corresponding p-aminobenzamides by any of a number of reductive methods. The preferred procedure is the hydrogenation procedure which may be identical with or equivalent to the conditions taught as reaction B in the above patent. Generally, the p-nitrobenzamide is hydrogenated under low pressure in a non-reactive solvent such as an alcohol, especially ethanol, in the presence of a catalyst, such as palladium on charcoal. The reaction is generally complete in about 2–4 hours.

Accordingly, another aspect of the invention is a process for preparing a compound of formula (I), or a pharmaceutically acceptable salt thereof which comprises hydrogenating a compound of formula (II), and, if applicable, salifying the product.

Alternatively, the p-nitrobenzamide intermediates of formula II may be prepared, for example, from p-nitrobenzoic acid ester derivatives of III (e.g., where X is OCH_3) upon reaction with IV. This aminolysis reaction is generally known and is preferably accomplished by heating the two reactants in a non-reactive solvent such as an alcohol, at temperatures from about 40-100°C. Anhydrides of p-nitrobenzoic acid may also be employed in the reaction with the amines of Formula IV. In addition, p-nitrobenzoic acid may be reacted with the required amine in the presence of coupling reagents such as DCC, EEDQ, CDI, etc.

The intermediates of Formulas III and IV and other necessary reagents are commercially available, are known in the art, or can be prepared by methods taught in the literature.

The p-aminobenzamides of this invention are anticonvulsant agents and may be administered by various routes including the oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes, being usually employed in the form of a pharmaceutical composition. It is a special feature of these compounds that they are effective following oral administration. The invention includes a pharmaceutical composition comprising from about 1% to about 95% by weight of a p-aminobenzamide of Formula I, or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable carrier.

In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to 500 mg, more usually 25 to 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic ef-

fect, in association with the required pharmaceutical carrier.

The active compounds are effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.5 to 300 mg/kg of body weight. In the treatment of adult humans, the range of about 1 to 50 mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, the chosen route of administration, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

The following examples further illustrate the preparation of the intermediates, compounds, and formulations of this invention.

Preparative Example 1

3,5-Dimethyl-N-[(2-methylphenyl)methyl]-4-nitrobenzamide.

A solution of 3,5-dimethyl-4-nitrobenzoyl chloride in tetrahydrofuran, generated from 7.0 g of 3,5-dimethyl-4-nitrobenzoic acid by standard procedures, was added to 4.3 g of 2-methylbenzyl amine and 5.0 ml of triethylamine in tetrahydrofuran. The reaction was stirred at ambient temperature overnight, chilled, and filtered. The filtrate was evaporated in vacuo and the residue therefrom was dissolved in chloroform, washed sequentially with 1N hydrochloric acid, 1N sodium hydroxide, water, and a saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated in vacuo. Crystallization from methanol/water provided 4.7 g of the desired title product, m.p. 202–203°C.

Analysis for $C_{17}H_{18}N_2O_3$:
Calculated: C, 68.44; H, 6.08; N, 9.39;
Found: C, 68.28; H, 6.01; N, 9.43.

Examples 2–3

The following intermediates were prepared from the appropriate acid chloride and corresponding amine according to the procedure of Example 1.

2. N-(2,6-dimethylphenyl)-3-methyl-4-nitrobenzamide, 49% yield, m.p. 175–177°C.
Analysis for $C_{16}H_{16}N_2O_3$:
Calculated: C, 67.59; H, 5.67; N, 9.85;
Found: C, 67.48; H, 5.54; N, 9.69.

3. 3,5-Dimethyl-4-nitro-N-(2,6-dimethylphenyl)benzamide, 65% yield, m.p. 250–252°C.
Analysis for $C_{17}H_{18}N_2O_3$:
Calculated: C, 68.44; H, 6.08; N, 9.39;
Found: C, 68.44; H, 5.92; N, 9.11.

Preparative Example 4

(R,S)-4-amino-3-methyl-N-(1-phenylethyl)benzamide hydrochloride.

A solution of 7.5 g of (R,S)-3-methyl-4-nitro-N-(1-phenylethyl)benzamide in 200 ml of ethanol/tetrahydrofuran was hydrogenated over 5% palladium on carbon. After the theoretical amount of hydrogen was consumed, the mixture was filtered and the filtrate evaporated. The residue was dissolved in a small volume of ethanol, approximately 1.5 molar equivalents of concentrated hydrochloric acid were added, and diethyl ether was added until cloudy. After standing overnight, 6.1 g of the title product were recovered by filtration, m.p. 200–201°C.
Analysis for $C_{16}H_{17}N_2O{\cdot}HCl$;
Calculated: C, 66.32; H, 6.26; N, 9.67; Cl, 12.23;
Found: C, 66.52; H, 6.36; N, 9.76; Cl, 11.97.

Examples 5–6

The following compound were prepared by the method of Example 4 from the corresponding nitro intermediates previously described.

5. 4-Amino-N-(2,6-dimethylphenyl)-3-methylbenzamide, 70% yield, m.p. 269–270°C.
Analysis for $C_{16}H_{18}N_2O$:
Calculated: C, 75.56; H, 7.13; N, 11.01;
Found: C, 75.31; H, 6.95; N, 10.73.

6. 4-Amino-N-(2,6-dimethylphenyl)-3,5-dimethylbenzamide, 80% yield, m.p. 167–169°C.
Analysis for $C_{17}H_{20}N_2O$:
Calculated: C, 76.09; H, 7.51; N, 10.44;
Found: C, 75.87; H, 7.28; N, 10.28.

The following formulation examples may employ as active compounds any of the pharmaceutical compounds of the invention or their pharmaceutically acceptable salts.

Example 7

A tablet formula is prepared using the ingredients below:

	Quantity (mg/tablet)
4-Amino-3,5-dimethyl-N-(2,6-dimethylphenyl)-benzamide hydrobromide	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5

The components are blended and compressed to form tablets each weighing 665 mg.

Example 8

Tablets each containing 60 mg of active ingredient are made up as follows:

4-Amino-3,5-dimethyl-N-(2,6-dimethylphenyl)benzamide	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50–60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

The compounds of Formula I are anticonvulsant agents with a high therapeutic ratio and long half-life and are therefore useful in the treatment and prevention of convulsions in mammals. Moreover, the anticonvulsant compounds of this invention, in contrast to anticonvulsant benzamides taught in the art, do not cause hemolysis. The compounds are effective against tonic extensor seizures elicited by maximal electroshock and should therefore be useful for treating generalized tonic-clonic ("grand mal"), cortical focal, complex partial (temporal lobe epilepsy), simple partial (focal motor), and post-traumatic seizures in humans. This activity is demonstrated in the electroshock induced convulsion inhibition assay which follows.

In the electroshock induced convulsion inhibition assay (E.S.), the compound to be tested was suspended in acacia and administered by gavage to each of ten Cox standard strain albino male mice (18–24 g) at the dose level being investigated. Thirty to 180 minutes after compound administration, the mice were subjected to a 0.1 second, 50 milliampere electroshock through corneal electrodes. The animals were examined and evaluated immediately after the electroshock for the occurrence of clonic, flexor tonic, or extensor tonic convulsions, or death and the ED_{50} was determined for each compound as the dose which inhibited the occurrence of extensor tonic convulsions in one half of the animals immediately after the electroshock. For comparison, 18 milliamperes was usually sufficient to produce extensor tonic convulsions in about half of the control animals; at 50 milliamperes, almost all control animals (receiving vehicle only) died. The test results summarized in Table I are reported as the ED_{50} values at the time interval found to provide an optimal response after dosing.

Table I

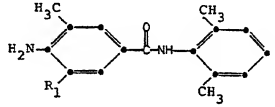
Anti-convulsant Activity of compounds of Formula I

Example No.	Electroshock ED_{50} (mg/kg)*	Time After dosing (minutes)**
5	3.8	60
6	5.6	60

*oral dose (gavage)-See text for methodology.
**Time (between dosing and administration of the electroshock) providing an optimal response.

Claims for the Contracting States: BE, CH, DE, FR, GB, IT, LI, NL, SE

1. A compound of the Formula



I

wherein
R_1 is hydrogen or methyl;
or a pharmaceutically acceptable acid addition salt thereof.

2. The compound of claim 1 which is 4-amino-3-methyl-N-(2,6-dimethylphenyl)benzamide or a pharmaceutically acceptable acid addition salt thereof.

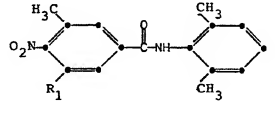
3. The compound of claim 1 which is 4-amino-3,5-dimethyl-N-(2,6-dimethylphenyl)benzamide or a pharmaceutically acceptable acid addition salt thereof.

4. A pharmaceutical formulation which comprises a compound of claim 1 in association with a pharmaceutically acceptable carrier or diluent.

5. A formulation according to claim 4 employing 4-amino-3-methyl-N-(2,6-dimethylphenyl)benzamide or a pharmaceutically acceptable acid addition salt thereof.

6. A formulation according to claim 4 employing 4-amino-3,5-dimethyl-N-(2,6-dimethylphenyl)benzamide or a pharmaceutically acceptable acid addition salt thereof.

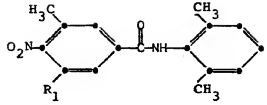
7. A compound of the formula



II

wherein
R_1 is hydrogen or methyl.

8. A process for preparing a compound of formula I, as claimed in claim 1, or an acid addition salt thereof, which comprises hydrogenating a p-nitro-benzamide of formula II



II

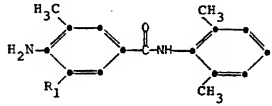
and, if applicable, salifying the product.

9. A compound of formula (I), as claimed in claim 1, for use as an anticonvulsant.

10. Use of a compound of formula (I) for the manufacture of an anticonvulsant.

Claims for the Contracting State: AT

1. A process for preparing a compound of formula (I)

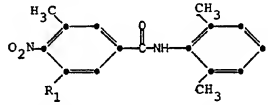


I

wherein

R_1 is hydrogen or methyl;

or a pharmaceutically acceptable acid addition salt thereof, which comprises hydrogenating a compound of formula (II)



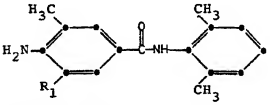
II

and, if applicable, salifying the product.

2. The process of claim 1 wherein N-(2,6-dimethylphenyl)-3-methyl-4-nitrobenzamide is hydrogenated.

Patentansprüche für die Vertragsstaaten BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Verbindung der Formel I



I

worin R_1 Wasserstoff oder Methyl bedeutet,

oder ein pharmazeutisch annehmbares Säureadditionssalz hiervon.

2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß es sich hierbei um 4-Amino-3-methyl-N-(2,6-dimethylphenyl)benzamid oder ein pharmazeutisch annehmbares Säureadditionssalz hiervon handelt.

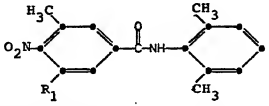
3. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß es sich hierbei um 4-Amino-3,5-dimethyl-N-(2,6-dimethylphenyl)benzamid oder ein pharmazeutisch annehmbares Säureadditionssalz hiervon handelt.

4. Pharmazeutische Formulierung, dadurch gekennzeichnet, daß sie eine Verbindung nach Anspruch 1 als Wirkstoff in Verbindung mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel enthält.

5. Formulierung nach Anspruch 4, dadurch gekennzeichnet, daß sie 4-Amino-3-methyl-N-(2,6-dimethylphenyl)benzamid oder ein pharmazeutisch annehmbares Säureadditionssalz hiervon als Wirkstoff enthält.

6. Formulierung nach Anspruch 4, dadurch gekennzeichnet, daß sie 4-Amino-3,5-dimethyl-N-(2,6-dimethylphenyl)benzamid oder ein pharmazeutisch annehmbares Säureadditionssalz hiervon als Wirkstoff enthält.

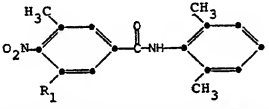
7. Verbindung der Formel II



II

worin R_1 Wasserstoff oder Methyl bedeutet.

8. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1 oder eines Säureadditionssalzes hiervon, dadurch gekennzeichnet, daß ein p-Nitrobenzamid der Formel II



II

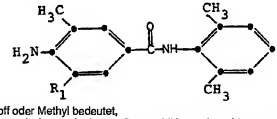
hydriert wird und das erhaltene Produkt gegebenenfalls in ein Salz überführt wird.

9. Verbindung der Formel I nach Anspruch 1 zur Verwendung als antikonvulsives Mittel.

10. Verwendung der Verbindung der Formel I zur Herstellung eines antikonvulsiven Mittels.

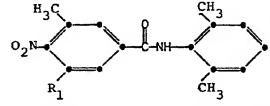
Patentansprüche für den Vertragsstaat AT

1. Verfahren zur Herstellung einer Verbindung der Formel I



I

worin R_1 Wasserstoff oder Methyl bedeutet,
oder eines pharmazeutisch annehmbaren Säureadditionssalzes hiervon, dadurch gekennzeichnet, daß eine Verbindung der Formel II



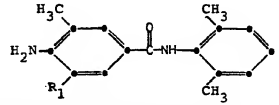
II

hydriert wird und das erhaltene Produkt gegebenenfalls in ein Salz überführt wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß N-(2,6-Dimethylphenyl)-3-methyl-4-nitrobenzamid hydriert wird.

Revendications pour les Etats Contractants BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Composé de formule:



I

dans laquelle R_1 représent un atome d'hydrogène ou un groupe methyle;
ou un de ses sels d'addition d'acides, pharmaceutiquement acceptable.

2. Composé selon la revendication 1, ce composé étant le 4-amino-3-méthyl-N-(2,6-diméthylphényl)benzamide, ou un de ses sels d'addition d'acides, pharmaceutiquement acceptable.

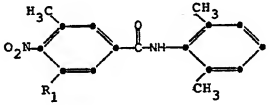
3. Composé selon la revendication 1, ce composé étant le 4-amino-3,5-diméthyl-N-(2,6-diméthylphényl)benzamide, ou un de ses sels d'addition d'acides, pharmaceutiquement acceptable.

4. Formulation pharmaceutique constituée d'un composé selon la revendication 1, en association avec un support ou un diluant pharmaceutiquement acceptable.

5. Formulation selon la revendication 4, cette formulation faisant appel au 4-amino-3-méthyl-N-(2,6-diméthylphényl)benzamide, ou à un de ses sels d'addition d'acides, pharmaceutiquement acceptable.

6. Formulation selon la revendication 4, cette formulation faisant appel au 4-amino-3,5-dimethyl-N-(2,6-diméthylphényl)benzamide, ou a un de ses sels d'addition d'acides, pharmaceutiquement acceptable.

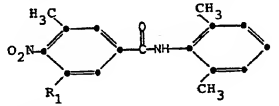
7. Composé de formule:



II

dans laquelle
R_1 représent un atome d'hydrogene ou un groupe méthyle.

8. Procédé de préparation d'un composé de formule I, selon la revendication 1, ou d'un de ses sels d'addition d'acides, ce procédé consistant à hydrogéner un p-nitrobenzamide de formule II



II

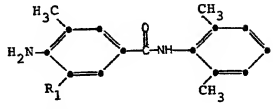
et, s'il y a lieu, à salifier le produit.

9. Composé de formule (I), selon la revendication 1, pour être utilisé comme agent anticonvulsivant.

10. Utilisation d'un composé de formule (I), pour la préparation d'un agent anticonvulsivant.

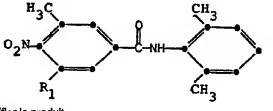
Revendications pour l'Etat Contractant AT

1. Procédé de préparation d'un composé de formule (I)



I

dans laquelle
R_1 représent un atome d'hydrogène ou un groupe méthyle;
ou d'un de ses sels d'addition d'acides, pharmaceutiquement acceptable, ce procédé consistant à hydrogéner un composé de formule (II)



II

et, s'il y a lieu, à salifier le produit.

2. Procédé selon la revendication 1, caractérisé en ce que l'on soumet le N-(2,6-diméthylphényl)-3-méthyl-4-nitrobenzamide à une hydrogénation.